Pediatric Diabetes Practice Recommendations

Presented by:
Carol Foster, MD
Professor
University of Utah
Department of Pediatrics/Endocrinology

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Goals

- Understand principles of diabetes care for pediatric patients including:
  - Initial screening and diagnostic criteria
  - Initial medical management and family education
  - Ongoing medical management and education
- Define and monitor outcome measures
  - Patient health outcomes
  - Care Management for those in poor control

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Overview

- Review of type 1 and type 2 diabetes
  - Pathophysiology
  - Diagnosis
- Initial treatment of child/adolescent with diabetes
  - Education
  - Medical
- Long term care of child with diabetes
  - Education
  - Technology
  - Complications

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Diabetes Mellitus

- Second most common chronic illness of childhood
- Two Major Forms
  - Type 1 Diabetes—requires insulin
  - Type 2 Diabetes—may respond to life style change and oral medication

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Type 1 Diabetes

- Immune mediated β-cell destruction leading to absolute insulin deficiency
- Most common type in children and adolescents
- Most common type in caucasians

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Type 2 Diabetes Mellitus

- Often Preceded by "Pre-diabetes": a state of relative insulin resistance
- Diabetes occurs when the pancreatic beta cells can no longer produce sufficient insulin to maintain a normal blood glucose
- Becoming epidemic in some areas of the country paralleling the increase in obesity in adolescents

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Other Forms of Diabetes

- Cystic Fibrosis-Related Diabetes
- Genetic Defects in Insulin Secretion
  - 3 or more generations of diabetes
- Gestational Diabetes
- Neonatal Diabetes
  - Often related to mutations in the "sulfonylurea receptor"

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PCMC Population
Distribution by Diagnostic Codes

ICD9 Code	Description	Count
250.01	Diabetes Type I, Juvenile	904
250.03	Diabetes Type I, Juvenile, Uncontrolled	385
250.00	Diabetes Type II, Adult	11
250.02	Diabetes Type II, Adult, Uncontrolled	9

2004 data: 1250-1300 unique patients, 3500 visits

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Criteria to Diagnose Diabetes

- Symptoms of diabetes plus random plasma glucose $\geq$ 200mg/dl (11.1 mmol/l)

  or
- Fasting plasma glucose $\geq$ 126 mg/dl (7.0 mmol/l)

  or
- 2 hour plasma glucose $\geq$ 200 mg/dl during OGTT.
  - WHO criteria, glucose load of 1.75 gm/kg or max of 75 gm glucose in water

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Characterization of Diabetes

	Type 1	Type 2
Age	Child / Adolescent	Adolescent
Habitus	Lean*	Heavy
Acanthosis	No	Yes
Family history/ Ethnicity	Uncommon (5%)/ Caucasion	Common (74-100%) / Non-white
DKA / onset	Common / rapid	Uncommon / insidious
Insulin dependent	Lifelong	Episodic
Autoimmunity	Common (80% +)	Uncommon (70% -)

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Increasing Incidence of Diabetes

- Type 1 increasing 3-5% per year worldwide
  - Most common in Caucasians
  - Not yet predictable, not preventable
- Type 2 increasing with increasing obesity
  - Prediction: 1/3 of all Hispanic children born in 2003 will develop type 2 diabetes
  - More common in Hispanics and African Americans, but occurs in all ethnicities
  - Predictable and preventable (?)

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Diabetes Screening: Who

- Symptomatic Child
  - Polyuria, polydipsia
  - Weight Loss
  - Fatigue
  - Vomiting, abdominal pain
  - Kussmaul Breathing
  - Lethary, confusion

- Asymptomatic with Risk for Type 2
  - Age 10 or onset of puberty
  - Overweight: BMI> 85%tile
  - Two risk factors:
    - Family History
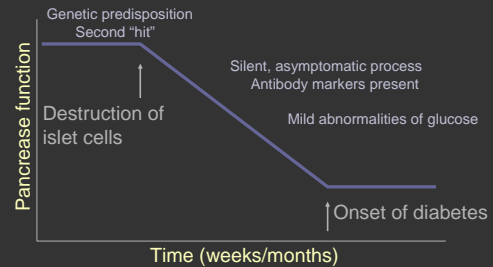   - High Risk Ethnicity
    - Signs of Insulin Resistance

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Diabetes Screening: How

- Obtain a Random Plasma Glucose
  - $\geq$ 200 mg/dL
    - Symptoms = Diabetes
  - 140 -199 mg/dL
    - Fasting Plasma glucose $\geq$ 126 = Diabetes
  - < 140 mg/dL
    - Other cause of symptoms
    - If high risk, start life style modifications

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Onset of Type 1 Diabetes

Genetic predisposition
Second "hit"

Silent, asymptomatic process
Antibody markers present

Pancrease function

Destruction of islet cells

Mild abnormalities of glucose

Onset of diabetes

Time (weeks/months)

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Screening: Trouble

- Symptoms + Glucose $\geq$ 200 mg/dL
  - Electrolytes, BUN, Creatinine
  - Check urine for ketones
- Serum pH < 7.35 or HCO3 $\leq$ 18 mEq/L
  - Manage as Diabetic Ketoacidosis

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Genetic Susceptibility

- Increased risk to first degree relatives
  - Risk increases 10 fold, to 5-10%
  - Risk greater if father has diabetes
- HLA type
  - HLA-D3/4 increased risk in Caucasians
  - DQA1*0301, DQB1*0302, DQA1*0501, DQB1*0201 loci confer increased risk in Caucasians
  - Different types may be associated with different age at presentation and course

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Type 1 or Type 2?

- Type 1
  - RPG $\geq$ 300 mg/dL
  - RPG < 300 mg/dL and ketones
  - Positive GAD Abs
  - Islet cell Abs (512)
- Type 2
  - RPG < 300 mg/dL and no ketones
  - Acanthosis nigracans
  - High Triglycerides
  - Family History
  - Ethnicity

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Type 1 Diabetes: Treatment

- Replacement of insulin
  - Must be administered by injection
  - Must be coordinated with food intake
- There is little usual routine anymore
  - Used to be 3 injections/day
  - Now at least 3 injections and may be as many as 7
  - Goal is to individualize therapy so as to incorporate diabetes into family life
- "Survival" Education

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Type 1 Diabetes Algorithm

- Start Insulin Based on Body Weight
- Long acting insulin once a day with Short acting insulin before meals

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Basal/Bolus Insulin for T1DM

- Glargine or Detemir makes up 40-60% of the Dose
- Novolog, Apidra, or Humalog before meals

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Rules of Thumb

- Calculate the Total Daily Dose (TDD) based on weight and severity of Illness
- Give half the TDD as long acting insulin
- Before Meal insulin: 500/TDD = grams of carbohydrate covered by 1 unit short acting insulin

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- Correction Dosing:
  - Give before meals, and no more often than every 3-4 hours
  - 1800/TDD = mg/dL 1 unit short acting insulin will decrease blood glucose

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Example: 50 kg boy ill for 6 weeks with initial glucose 500 and large urine ketones

- TDD = 50 kg
- Insulin glargine at 25 units once a day
- Insulin aspart at:
  - 500/50 or 1 unit per 10 grams carbohydrate before meals
  - 1800/50 or roughly 1 unit for every 50 mg/dL above 150 mg/dL to correct Blood glucose at meals

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- Our boy has a blood glucose of 300 mg/dL at lunch and wants to eat 60 grams of carbohydrate

- He takes 6 units insulin for food and 3 units as a correction dose or 9 units before the meal

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Survival Education: Keep it Simple

- C: Basic carbohydrate counting
- H: Hypoglycemia treatment
- U: Urine ketones when glucose high
- M: Monitor Blood glucose
- S: Shots

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Blood Glucose Goals and Age

- Children 6 and under
  - Avoid Low Blood Sugars and keep glucose 100 – 200 mg/dL
  - May need to give insulin after meals
- Children 7 through 12
  - Tighten control to 80 – 180 mg/dL before meals
- Adolescents
  - Tighten control to 70 – 150 mg/dL

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Utah Diabetes Center Approach

- Intensify control
  - DCCT results and impact upon long term complications
  - Mimic normal physiology
- Increase monitoring
  - Lunch time testing
  - More frequent testing
  - Testing at different times
- Increase insulin injections
- Increase flexibility

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Living with Diabetes

- Exercise lowers glucose and causes delayed hypoglycemia
  - Eat extra carbohydrates: 15 g for every 30 minutes of exercise
  - Decrease evening long-acting insulin by 10-20%
  - Check blood glucose at night

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Diabetes Management

- Check Blood Glucose Before Major Meals, at Bedtime and at 2 – 3 AM
- Give insulin before all major meals and for any snacks more than 15 grams of carbohydrate
- Correct high blood glucose values at meals and bedtime

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Diabetic Ketoacidosis

- State of absolute or relative insulin deficiency resulting in hyperglycemia and metabolic acidosis
  - Hyperglycemia - glucose >300 mg/dl
  - Acidosis - pH < 7.3
- Incidence is decreasing in new diagnosis
- Mortality is real, probably less than 1% in experienced hands, not always predictable

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Etiology of DKA

- Hormonally mediated factors:
  - Insulin deficiency results in catabolic state
  - Counterregulatory hormone excess which accelerates catabolism
    - Glucagon, cortisol, catacholamines, GH
  - Neither is sufficient
- Incidence: presenting event for 30-40% of new onset diabetes
  - Probably actually less with education
- Morbidity: 65% of all pediatric diabetic admissions

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Moderate Ketoacidosis

- May require IV fluids, but if not vomiting, try PO fluids
- Start with 10-20 cc/kg of Ringer's lactate or Normal Saline
- After bolus, check glucose
  - If before a meal, use SQ regimen
  - If not, give 0.1 to 0.2 Units/kg Short acting insulin SQ

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Managing Ketoacidosis

- Classify Ketoacidosis by Severity
  - Mild: pH 7.3 – 7.35 and HCO3 15 - 18
  - Moderate pH 7.2 – 7.3 and HCO3 10 - 15
  - Severe pH < 7.2 and HCO3 < 10

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Severe Ketoacidosis: IV Fluids

- IV volume expansion 20 cc/kg Ringer's Lactate or NS. Repeat for cardiovascular instability (shock)
- Start IV replacement at 1.5 x maintenance using ½ NS and 20-40 mEq/L KCl

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Mild Ketoacidosis

- Manage with Oral Hydration and Subcutaneous Insulin
- Ongoing laboratory assessment is not needed
- Use routine SQ insulin regimens

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Severe Ketoacidosis: Insulin

- IV insulin at 0.1 units/kg/h
- Reduce glucose 50 – 100 mg/dL/h
- Add dextrose when glucose reaches 150 – 250 mg/dL
- Unless true hypoglycemia, do not decrease insulin below 0.08 units/kg/h
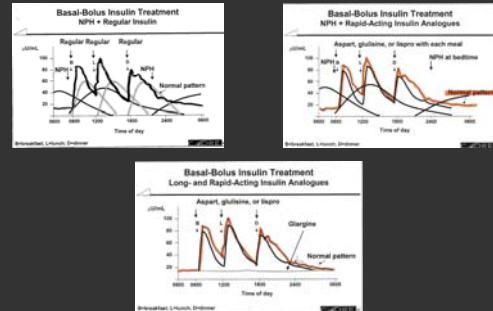
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Monitoring in Severe DKA

- Neuro Checks every 2 hours
- Glucose hourly
- Electrolytes every 2 hours

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Insulin Regimens

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When to call the ICU

- Clouded Consciousness
- Shock
- Other organ involvement
- Need for mechanical ventilation
- Inotrope infusion

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Insulin Dosing: Pump

- More intensive management than NPH
  - More flexibility
  - Similar to Lantus insulin
- CSII or insulin pump
  - Continuous sc infusion of short acting insulin
  - Requires calculation of both a carbohydrate dose for food and correction dose
- In event of pump malfunction, have only 3-4 hours of insulin coverage

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Outpatient Management of New Patients

- Initial education program
  - Pathophysiology and etiology
  - Insulin dosing, insulin injections, and meal planning
  - Treatment of emergencies
  - Living with Diabetes
- Outpatient phone contact frequently over the first 2-4 weeks
- Office visit to continue education at 2-4 weeks
  - Sick days and blood ketone testing, correction dosing, trend and pattern analysis

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Post Prandial Blood Sugars

- Increased awareness of role of Post-prandial blood sugars in elevating $HgbA_1C$
- Target of the DCCT: <180 mg/dl
  - Age dependent targets
    - Age <5 yo: <200 mg/dl
    - Age 5-11 yo: <180 mg/dl
    - Age 12-18 yo: < 150 mg/dl
  - Test 1-2 hours after eating

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Goals of Pediatric Care

- Enable children/teens to participate in all age appropriate activities with their peers
- Prevent long term complications
  - Maintain good to excellent control
- Risk:Benefit Ratio of Control
  - Minimize the episodes of hypoglycemia
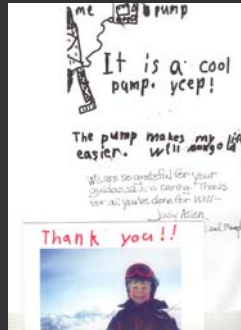
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Visit Frequency

- Target is 3-4 times per year
  - Is this reasonable give travel distances?
  - Is this reasonable with the number of trained diabetologists?
- Does a model utilizing more generalist involvement make sense?
  - Requires communication between colleaques
  - Requires education of generalists

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Long-term Management

- Routine monitoring of blood glucose
- Individualized insulin regimen
  - Chose regimen for best control with best risk:benefit profile
- Quarterly office appointment
  - Hgb A_1C, review of blood glucose records
- Regular educational updates from CDE re: blood glucose management, meal planning
- Complication screening
  - Sort term: Psychologic, thyroid, celiac, growth/develoment
  - Long term: Renal, Eye, Lipid, Neurologic

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Future Technology

- Pumps and meters that communicate
  - Bolus wizard software
  - "Beam" BG to pump
- Continuous sensor
- Insulin delivery
- Non-invasive BG monitors
- Cure
  - Immune system very complex
  - Good, low risk treatment means "cure" must be have excellent risk: benefit profile

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Outcome Measures

- Visit frequency
- Control
  - HgbA$_1$C: frequency of determination, absolute value
  - Growth
- Co-morbid conditions
  - Celiac disease (TTG), thyroid (TSH), hypertension (BP), lipid profile (LDL, triglycerides, total cholesterol)
- Monitoring for long term complications
  - Eye (dilated exam), renal (urine microalbumin:creatinine), cardiovascular (BP and lipid profile)

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Type 2 Diabetes

- Obesity driven
  - Not all obese teens have diabetes
- Treatment is prevention
  - Lifestyle changes
  - Weight control and exercise
  - Appropriate for all overweight children
    - Limit TV and video time
    - Limit junk food

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Incidence: Type 2 Diabetes

- Incidence is increasing
  - Incidence parallels the increasing obesity of children and teens
- Type 2 diabetes is the more common in African-American, Native American, Pacific Islander, and Hispanic children and teens
  - Genetic predisposition compounded by lifestyle
- Type 2 diabetes is caused by diet and lifestyle
  - Excess caloric intake, inadequate exercise
  - Obesity

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Progression of Type 2 Diabetes

⇑ Insulin resistance → ⇑ hyperinsulinism

↓ suppression of hepatic gluconeogenesis

Fasting and post-prandial hyperglycemia

Downregulation of insulin receptors & impairment of post-receptor events

⇑ Hyperglycemia → ⇓ Insulin secretion

Type 2 diabetes

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Etiology

- Puberty
  - GH is counter-regulatory hormone and increases peripheral insulin resistance
  - Insulin activity is 30% lower in Tanner 2-5 adolescents vs children and adults
- Obesity
  - Prevalence of overweight children from 1960-1980 was constant; but, from 1970-2000
    - 12-19 year olds: increased from 5% to 15%
    - 6-11 year olds: increased from 4% to 15%
- Focus on pubertal and peripubertal overweight children (> 10 years of age)
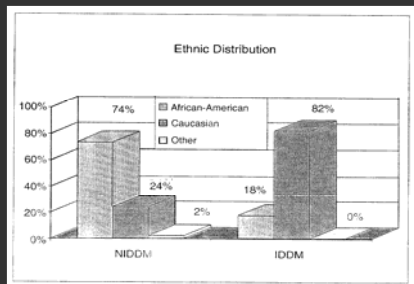
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Natural History of Type 2 Diabetes

Obesity   IFG*   Diabetes   Uncontrolled hyperglycemia
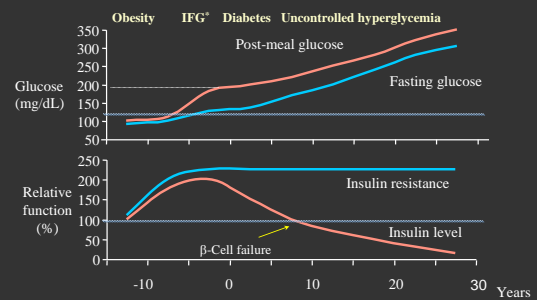
*IFG=impaired fasting glucose.

Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota.

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Type 2 DM and Ethnicity

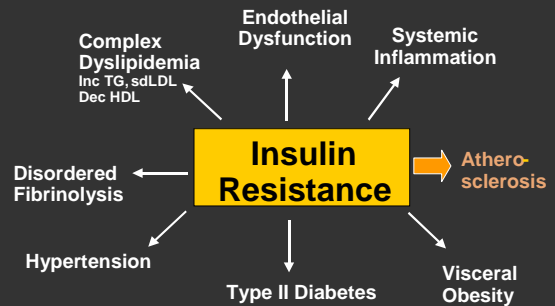

Pihoker et al - 1998

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The Metabolic Syndrome of Insulin Resistance

Complex Dyslipidemia
Inc TG, sdLDL
Dec HDL

Endothelial Dysfunction

Systemic Inflammation

Insulin Resistance

Disordered Fibrinolysis

Athero-sclerosis

Hypertension

Type II Diabetes

Visceral Obesity

Adapted from the Consensus Development Conference of the American Diabetes Association. *Diabetes Care* 1998;21:310-314.
Pradhan AD et al. *JAMA* 2001;286:327-334.

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Pharmacologic Therapy for Type 2 Diabetes

- Biguanides (metformin)
- Insulin (long, intermediate, short, very short, analogues, inhaled)
- �ख✗✗✗✗✗✗✗✗✗✗✗✗✗✗✗✗✗✗
- Sulfonylureas (glyburide, glipizide, glimepiride)
- Short acting Insulin Secretagogues (repaglinide, netaglinide)
- Alpha Glucosidase Inhibitors (acarbose, miglitol)
- Thiazoledinediones (rosiglitazone, pioglitazone)

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Biguanides (Metformin)

- Mechanism: decrease hepatic glucose production and improve peripheral insulin sensitivity
  - **Side effects: nausea, abdominal cramps, diarrhea**
- Contraindications: renal failure, hepatic failure, congestive heart failure, alcoholism
  - **Hold for dehydration, iodinated contrast studies**
- Advantage: little hypoglycemia, weight neutral
- Indications: Type 2 DM, PCO, Insulin resistance

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Medical Therapy:
metformin (Glucophage)

- FDA approved for use in children/teens > 10 yrs for diagnosis of type 2 diabetes
- Side effects:
  - Low risk of hypoglycemia
  - GI side effects are generally well tolerated if dose is increased gradually
  - Weight neutral; perhaps some weight loss (5kg)
- Check creatinine before starting and q year
- Hold for IV contrast or dehydration
- Consider pregnancy issues

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Insulin Therapy in Type 2

- Initially:
  - **Severe hyperglycemia, ketonuria**
  - **Protect teen from DKA while determining the type of diabetes**
  - **When other medications contraindicated, e.g. liver disease or chemotherapy, or peri-operative**
  - **Pregnancy**
- Later
  - **When β cell function no longer adequate and oral therapy is failing**

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Lifestyle Therapy

- First line of therapy
  - Potentially prevent type 2 diabetes in some teens??
- Nutrition
  - No medication will control blood glucose in the face of uncontrolled eating
  - Must have access to pediatric/adolescent nutritionists
  - Unlike current approach to type 1 diabetes, fat intake probably should be addressed initially
- Exercise
  - Increase peripheral glucose utilization by muscle, decrease body fat

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Screening Children and Adolescents: Who?

- Children over 10 yrs or in puberty with the who are overweight:
  - BMI > 85% for age and sex, weight for height > 85th%, weight >120% ideal for height
- And have 2 of the following risk factors
  - Family history in first or second degree relative
  - American Indian, African-American, Hispanic, Asian/Pacific Islander
  - Signs of insulin resistance: acanthosis nigricans, PCOS, hypertension, dyslipidemia

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Screening Children and Adolescents: How?

- Frequency: every 2 years
- Preferred test is the fasting plasma glucose

- Consider also:
  - 2 hour post prandial plasma glucose
    - may be abnormal before the fasting plasma glucose

Consensus statement from ADA, Pediatrics (/2000) 105: 671

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Complications

- Same complications that adults face
  - Cardiac disease
  - Neuropathy
  - Nephropathy
- Will the complications be more severe?
  - Earlier age of onset?????
  - Predisposition to be worse????

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Summary

- Incidence of type 2 diabetes in the pediatric population is increasing and it will become a significant source of morbidity and financial burden on our society – worldwide
- Prevention involves changing lifestyles and environment of our children and teens
- Treatment options are the same as those available for adults but with little or no research into safety and efficacy of these drugs in pediatric population

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Long Term Issues

- Aggressively maintaining control
  - Are the adult paradigms appropriate?
  - Hgb A_{1C}
  - Blood sugar testing
  - Weight control
- Management of lipid abnormalities
- Monitoring for cardiac disease at earlier ages
- Management during pregnancy

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Prevention

- Prevention is key
  - Delay onset in many cases, possibly eliminate in some
- Weight control
  - Exercise
  - Dietary: caloric and fat intake
  - Lifestyle: -48% vs untreated control
- Medications
  - Metformin: -31% vs untreated control

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Summary

- Prevention of type 2 diabetes = Prevention of Obesity
  - Absolutely necessary for us as a society
  - Behavioral changes, start now with simple steps
  - Need studies of medications to treat obesity in children and teens
- Treatment of type 2
  - Need studies of medications
    - Teens are not just little adults
  - Entire family needs to commit to treatment
  - Mental health issues and support

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